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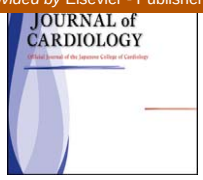

Original article

Effects of mineralocorticoid receptor antagonist spironolactone on atrial conduction and remodeling in patients with heart failure

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KEYWORDS
Conduction;
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Summary
Background: Spironolactone was shown to reduce mortality in patients with heart failure (HF). However, the effect of spironolactone on the incidence of atrial fibrillation remains unknown. Therefore, we examined the effects of spironolactone on atrial conduction and remodeling in patients with HF.
Methods and results: A total of 21 patients with HF were divided into either spironolactone group ($n = 11$) or control group ($n = 10$). The patients were followed up for 12 months. Blood examination, echocardiogram, and signal-averaged electrocardiogram were performed at study enrollment and after 3 and 12 months of treatment. In the spironolactone group, atrial natriuretic peptide tended to reduce, left atrium dimension was significantly smaller, the ratio of E wave to A wave tended to improve, and P-duration was significantly shortened.
Conclusions: Spironolactone improves atrial conduction and remodeling in patients with HF.

Introduction

Atrial fibrillation (AF) in patients with heart failure (HF) is generally considered a negative prognostic factor. Several studies have shown that activation of the renin—angiotensin—aldosterone system is associated with

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the mechanism of AF [1—3]. Angiotensin-converting enzyme (ACE) inhibitors and the angiotensin II type 1 (AT1) receptor antagonists have been shown to be effective in reducing the incidence of AF in addition to the rate of mortality in patients with HF [3—6]. However, the rate of AF in patients with HF remains relatively high despite the success achieved with ACE inhibitors and AT1 receptor antagonists in the treatment of AF. This high rate is partly due to the aldosterone (ALD) escape phenomenon [7—10].

ALD has an important role in the pathophysiology of HF [11—14]. In the Randomized Aldactone Evaluation Study (RALES), the mineralocorticoid receptor antagonist spironolactone was shown to reduce mortality in patients with HF, and the beneficial outcome in RALES was shown to be associated with the suppression of the marker of cardiac collagen synthesis by spironolactone [15]. Moreover, ALD levels have been found to increase with profound implications for left ventricular remodeling and long-term prognosis [16,17]. However, the effect of spironolactone on atrial conduction and remodeling remains unknown.

Therefore, in the present study, we examined the effects of spironolactone on atrial conduction and remodeling in patients with HF.

Methods

Patient population

We studied 21 patients with stable symptomatic HF [New York Heart Association (NYHA) functional class II or III] and left ventricular ejection fraction (LVEF) <40%. There were 15 men and 6 women (mean age, 68 years). The cause of HF was dilated cardiomyopathy in 14 patients and ischemic cardiomyopathy in 7 patients. Patients were excluded if they had primary operable valvular heart disease, congenital heart disease, unstable angina, renal failure, hyperkalemia, primary hepatic failure, or AF. On enrollment in the study, 21 patients were being treated with loop diuretics, 12 with ACE inhibitors, and 9 with AT1 receptor antagonists. All patients were being treated with ACE inhibitors or AT1 receptor antagonists. The antiarrhythmic drug amiodarone was used for prevention of ventricular tachycardia. Most of these drugs had been administered for >3 months.

Study protocol

All of the patients were in a stable condition for at least three months before enrollment. Fig. 1 shows the study protocol. The 21 patients with mild-to-moderate symptomatic left ventricular dysfunction were randomly divided into two groups that received treatment with spironolactone ($n = 11$) or no additional drug ($n = 10$). The dose of spironolactone was set at 25 mg once daily.

The patients were followed up for 12 months. Blood samples were collected from each patient at study enrollment and after 3 and 12 months of treatment. To measure the plasma levels of neurohumoral factors, blood samples were collected from an antecubital vein following supine rest for at least 30 min. Echocardiogram and signal-averaged electrocardiogram triggered by P waves (P-SAECG) were also performed at study enrollment and after 3 and 12 months of

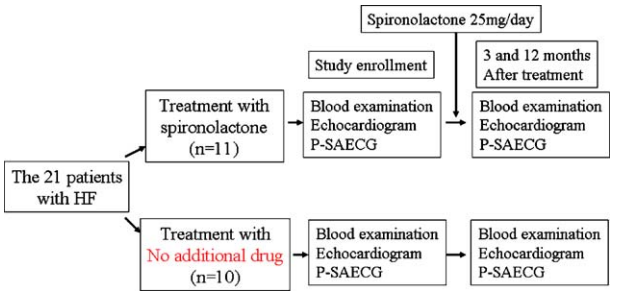

Figure 1 Study protocol. HF, heart failure; P-SAECG, signal-averaged electrocardiogram triggered by P waves.

treatment. Echocardiogram was performed with a 3.75-MHz transducer connected to an ultrasound system (Prosound SSD-4000, Aloka, Tokyo, Japan). The dimension and LVEF were determined by M-mode. The peak velocities of early (E) and late (A) mitral inflow were measured using pulse-wave Doppler with the sample volume at the tip of mitral valve leaflets.

Signal-averaged electrocardiogram triggered by P waves

P-SAECG was recorded using the MAC-5000 (GE Medical Systems, USA). This system uses P-wave for both triggering and matching with a template. Data are acquired for P-SAECG from the surface ECG in three mutually perpendicular axes of the Frank lead system. The X lead is from left to right mid axillary line at the fifth intercostal space. The Y lead is from head to foot, and the Z lead is from the sternum at fifth intercostal space to directly posterior. Signals were then amplified and digitized at a sampling rate of 1000 samples/s and a resolution of 1 μV.

A P-wave template was initially generated for P-wave matching using a 9-s window of raw data. After QRS and P-wave detection, a seed beat was automatically detected based on its matching with all other beats in the 9-s window of raw data. A template matching with the selected seed beat was performed within these data. All P-waves that met the criteria of P-wave matching were then averaged for a template.

In the averaging phase, QRS detection was performed first, and then QRS-T portion was subtracted. P-waves were detected in a window ranging from previous T-wave offset to the current QRS onset points from a composite absolute value of band-pass filtered and first-differenced X, Y, and Z signals. Qualified P-waves with accepted P duration and correlation coefficient >0.95 were averaged. The averaging process continued until either the target number of beats (250—400) or the desired noise level of <0.3 μV was achieved.

The averaged P-wave signals were filtered by a spectral band-pass filter with a bandwidth of 40—250 Hz, and then combined into a vector magnitude using the formula $(X^2 + Y^2 + Z^2)^{1/2}$. The P-wave delineation was performed on the vector magnitude. The P-SAECG measurements included filtered P-wave duration (P-dur) and the voltage of the root mean square (RMS) in microvolts (Fig. 2). The RMS voltage is the RMS of the spatial magnitude over an interval. We mea-

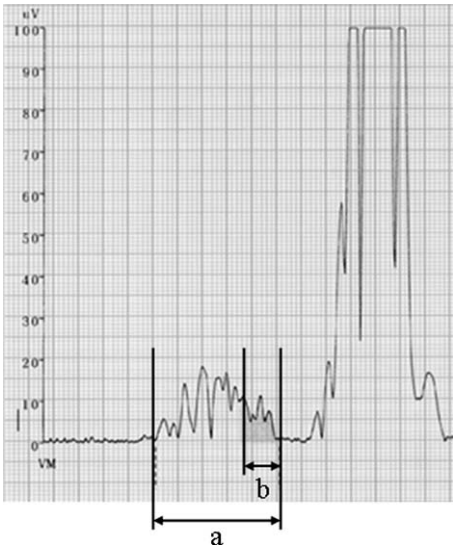

Figure 2 Signal-averaged electrocardiogram triggered by P waves. (a) Filtered P-wave duration. (b) The voltage of the root mean square.

sured the RMS voltage for 30 ms of the filtered P-wave of the spatial magnitude and its duration.

Statistical analysis

Results are expressed as the mean ± SD. Continuous values were compared with analysis of variance. Comparison between two groups at each time was performed using unpaired *t* test. Comparison within the groups at each point was performed using paired *t* test. Categorical data were compared against a chi-squared distribution. A *p*-value < 0.05 was regarded as significant.

Results

Clinical characteristics

Table 1 shows the clinical characteristics before treatment. There were no differences in age, gender, etiology of heart failure, LVEF, or medications on entry into the study between the spironolactone group and the control group.

Comparison of neurohumoral factors before and after treatment

Table 2 shows neurohumoral factors before and after treatment. There were no differences in pretreatment neurohumoral factors, such as ALD, plasma renin activity (PRA), atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP) between the spironolactone group and the control group. In the control group, there were no significant changes in these variables after 3 and 12 months. In the spironolactone group, ALD and PRA significantly increased, and ANP and BNP tended to reduce after treatment. The serum potassium concentration did not change in the control group during 12 months. During the same period, however, the serum potassium concentration in the spironolactone group increased by 0.5 mmol per liter. The difference in the serum potassium concentration between the two groups was not significant and was not clinically important.

Comparison of echocardiographic variables before and after treatment

Table 3 shows echocardiographic variables before and after treatment. There were no differences of pretreatment echocardiographic variables, such as left ventricular end-diastolic dimension (LVEDd), LVEF, left atrium dimension (LAd), and peak velocities of early (E) and late (A) mitral inflow between the spironolactone group and the control group. In the control group, there were no significant changes in LVEDd and LAd after treatment. However, LVEDd and LAd in the spironolactone group were significantly smaller after 12 months. The differences in LVEDd and LAd between the two groups after 12 months were significant. The LVEF in the control group significantly became worse, however, the LVEF in the spironolactone group tended to improve after 12 months. Furthermore, the A wave and the ratio of E wave to A wave (E/A) tended to improve after 12 months in the spironolactone group.

Comparison of P-SAECG variables before and after treatment

Fig. 3 shows P-SAECG variables before and after treatment. There were no differences of pretreatment P-dur and RMS between the spironolactone group and the control group. In

Table 1 Clinical characteristics.

	Control group	Spironolactone group	
Age (years)	68 ± 7	67 ± 8	N.S.
Gender (men/women)	7/3	8/3	N.S.
Etiology (ICM/DCM)	7/3	7/4	N.S.
LVEF (%)	36 ± 6	34 ± 6	N.S.
ACEI (%)	60	55	N.S.
ARB (%)	40	45	N.S.
β blocker (%)	80	82	N.S.
Antiarrhythmic drug (%)	20	18	N.S.

ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2 Neurohumoral factors before and after treatment.

	Study enrollment	3 months	12 months
Aldosterone (ng/dl)			
Control	5.8 ± 1.1	5.5 ± 0.9	6.3 ± 1.1
Spironolactone	7.2 ± 1.9	13.5 ± 2.6[#,$]	14.8 ± 3.2[#,$]
PRA (ng/ml/h)			
Control	2.4 ± 0.4	2.5 ± 0.3	4.4 ± 1.9
Spironolactone	4.4 ± 1.9	13.2 ± 4.1[#,$]	13.1 ± 4.8[#,$]
ANP (pg/ml)			
Control	45 ± 11	44 ± 10	50 ± 10
Spironolactone	77 ± 38	55 ± 27	48 ± 17
BNP (pg/ml)			
Control	120 ± 27	121 ± 27	156 ± 36
Spironolactone	128 ± 36	107 ± 33	95 ± 29
K (mEq/l)			
Control	4.2 ± 0.2	4.1 ± 0.2	4.3 ± 0.2
Spironolactone	4.0 ± 0.2	4.3 ± 3.1[#]	4.5 ± 0.2[#]
Hematocrit (%)			
Control	42 ± 5	40 ± 5[#]	40 ± 4
Spironolactone	39 ± 5	41 ± 5[#]	39 ± 4

PRA, plasma renin activity; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.
[#] $p < 0.05$ (comparison within the groups at each point).
[$] $p < 0.05$ (comparison between the two groups at each time).

the control group, there were no significant changes in P-dur and RMS after 3 months. However, in the spironolactone group, P-dur was significantly shortened and RMS was significantly higher after 3 months. The differences in P-dur and RMS between the two groups were significant and continued at least during 12 months.

Discussion

This study has demonstrated that spironolactone improves atrial conduction and remodeling in patients with HF. The major findings of this study were that ANP and E/A tended to reduce, LAd was significantly smaller, and

Table 3 Echocardiographic variables before and after treatment.

	Study enrollment	3 months	12 months
LVEDd (mm)			
Control	57 ± 6	58 ± 6	59 ± 7[#]
Spironolactone	61 ± 4	59 ± 5[#]	57 ± 5[#]
LVEF (%)			
Control	36 ± 6	35 ± 5	33 ± 7[#]
Spironolactone	34 ± 6	34 ± 6	37 ± 8
LAd (mm)			
Control	40 ± 6	40 ± 7	43 ± 7
Spironolactone	42 ± 3	40 ± 4	37 ± 3[#,$]
A (cm/s)			
Control	72 ± 14	69 ± 18	69 ± 14
Spironolactone	65 ± 21	70 ± 19	72 ± 16
E/A			
Control	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.3
Spironolactone	1.4 ± 0.4	0.8 ± 0.3	0.7 ± 0.3
IVC (mm)			
Control	12 ± 2	12 ± 2	13 ± 4
Spironolactone	13 ± 3	11 ± 2[#]	12 ± 2

LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; Lad, left atrium dimension; E, peak velocities of early mitral inflow; A, peak velocities of late mitral inflow; IVC, inferior vena cava dimension.
[#] $p < 0.05$ (comparison within the groups at each point).
[$] $p < 0.05$ (comparison between the two groups at each time).

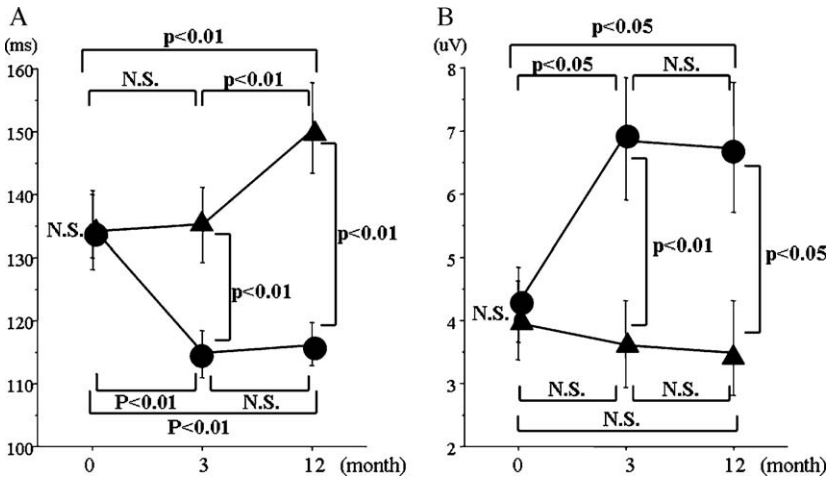

Figure 3 Comparison of P-SAECG variables before and after treatment. In the spironolactone group, filtered P-wave duration (A) was significantly shortened and the voltage of the root mean square (B) was significantly higher after 3 months. The differences in filtered P-wave duration and the voltage of the root mean square between the two groups were significant and continued at least during 12 months. P-SAECG, signal-averaged electrocardiogram triggered by P waves. Error bars represent 95% confidence intervals. Circles = spironolactone group; triangles = control group.

P-dur was significantly shortened in the spironolactone group.

Mechanisms

Several possible mechanisms exist by which spironolactone may improve atrial conduction and remodeling. These include decrease of wall stress, modulation of refractoriness, interference with ion currents, modification of sympathetic tone, and stabilization of electrolyte concentrations [18—23].

Atrial stretch and spironolactone

We have no data to explain the underlying mechanism of the finding in our study. However, increasing evidence suggests that atrial stretch induced by increased atrial pressure may precipitate AF through an effect on atrial refractoriness [23,24]. Bauersachs et al. showed that the addition of spironolactone to ACE inhibition in HF significantly increased urinary sodium and volume excretion, leading to reduced filling pressures [25]. Our data conform to the hypothesis that the reduction of intravascular volume (as suggested by the reduction of inferior vena cava dimension and increase of hematocrit) by spironolactone may reflect the diuretic action of spironolactone. Furthermore, reduced plasma levels of ANP in patients with HF treated with spironolactone may indicate a reduced preload, leading to improve atrial stretch in the present study.

Atrial remodeling and spironolactone

Several studies have shown a positive correlation between atrial enlargement and the incidence of AF [26—29]. Petersen et al. compared the left atrial size, as determined by echocardiography, in patients in sinus rhythm with that of patients with AF [26]. The atria in sinus rhythm were smaller than that of patients with AF. For many years, it has been discussed whether atrial enlargement is the cause or a consequence of AF. However, the high incidence of AF in the presence of mitral stenosis and/or mitral insufficiency strongly suggests atrial dilatation to be a cause of AF [27,28]. In the present study, LAd in the spironolactone group was significantly smaller after 12 months. Furthermore, spironolactone prevents myocardial fibrosis by blocking the effects of ALD on the formation of collagen. It may be a cause of improvement of RMS in the spironolactone group in the present study.

Atrial conduction and spironolactone

AF is multifactorial, one of the suggested mechanisms being multiple microreentry. By definition of reentry, depressed conduction is required for the occurrence of AF [30,31]. It was reported that the atrial conduction abnormalities in patients with lone paroxysmal AF (PAF) could be detected by SAECG P-wave, and this could be utilized as a noninvasive method for detection of patients at risk for lone PAF [32]. In addition, studies showed that prolonged filtered P-wave duration in sinus rhythm is considered to indicate an increased risk for PAF in patients with and without structural heart disease [33—35].

HF is not only associated with severe structural and functional changes of the atria, but also related to electrophysiologic abnormalities. Hemodynamic atrial changes may cause depressed atrial conduction, fragmented atrial activity, and multiple atrial stimulation foci that could predispose to AF [36]. Depressed atrial conduction prolongs atrial activation time and that prolongs P wave. Fragmented atrial activity causes low amplitude late potentials on the terminal portion of the P wave. P-wave signal-averaged ECG technique can detect the duration and the terminal segment amplitude of the P wave. Therefore, with the P-SAECG technique, PAF risk can be detected.

Experimental studies have shown that acute atrial stretch prolongs the conduction time and increases spatial heterogeneities in conduction [37,38]. In a canine model of HF, interstitial fibrosis and heterogeneous conduction were considered important determinants of the substrate for AF [39]. In human studies as well, atrial dilatation and impaired conduction were correlated with atrial arrhythmias [40—42]. A reduced conduction velocity shortens the wavelength and thereby could stabilize AF. In our present study, the reduction of atrial stretch and the inhibition of atrial remodeling by spironolactone were associated with the improvement of atrial conduction, leading to improve P-dur and RMS.

Clinical implications

Increased interest in and the use of spironolactone have resulted from clinical trials demonstrating decreased mortality in patients with HF treated with spironolactone. The current study offers important new mechanistic insights into the effects of spironolactone in HF, providing novel information about its role in modulation of atrial electrophysiology and left ventricular function. AF is common in patients with HF and associated with increased morbidity and mortality, but their treatment remains less than optimal. Our data open an entirely new potential and promising role for spironolactone in the prevention of AF in patients with HF. Furthermore, PRA and ALD levels began to increase by treatment with spironolactone, suggesting blockade of ALD receptors and positive neurohormonal feedback. Therefore, combination therapy with ACE inhibition is very important. However, the problem of hyperkalemia is also important in patients treated with combination therapy. Previous studies suggested that combination therapy began at a dose of 25 mg/day of spironolactone. In the present study, at a dose of 25 mg of spironolactone, the serum potassium concentration in the spironolactone group increased by 0.5 mmol per liter, but it was not clinically important.

Limitations

The primary limitation of this study is the small study population of only 21 patients. Without the power estimation and due to the low number of patients included, the study must be regarded as a pilot study. Therefore, further studies are needed to assess the effects of spironolactone in patients with HF. In addition, the present study employed a fixed spironolactone dose of 25 mg/day, therefore, the dose—response effect of spironolactone on atrial conduction and remodeling must also be evaluated.

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